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CLASSICAL PERSPECTIVES

One hundred years of pulmonary function testing: a perspective on 'The diffusion of gases through the lungs of man' by Marie Krogh

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The single breath carbon monoxide (CO) diffusing capacity test (D_{LCO}; or transfer factor T_{LCO}) measures the alveolar surface area available for gas exchange from the alveolar volume and the rate of alveolar CO uptake (Hughes & Bates, 2003). It is now a test that is carried out hundreds of thousands of times a year in pulmonary function laboratories across the globe, benefiting millions of respiratory patients. The principles and application of the single breath D_{LCO} test were first described in experiments published by Marie Krogh 100 years ago in *The Journal of Physiology* (Krogh, 1915). To understand the clinical and research impact of these studies it is first necessary to consider the context in which they were performed.

Secretion *vs.* diffusion theory

In the 1890s there was controversy regarding the mechanism of alveolar gas exchange. Christian Bohr and John Scott Haldane, key physiologists of the time, had recorded the oxygen tension in arterial blood as being higher than that in alveolar gas, giving rise to the suggestion that oxygen transport was active. August Krogh joined Bohr's laboratory in 1987; employed as a teaching assistant he completed his PhD on respiration of frogs in 1903. Marie Jorgensen joined the laboratory in 1904 and together they worked on a series of studies to investigate the rate of oxygen transport across the lung epithelium. August Krogh was able to greatly improve the accuracy of measurements of arterial P_{O_2} (Krogh, 1908), and using these new techniques, to their surprise, they were *unable* to support Bohr's theory of gas secretion, always finding that alveolar P_{O_2} was higher than arterial P_{O_2} (Krogh & Krogh, 1909*a*). This led to a delay in the publication of their findings while they tried to reconcile the discrepancy in the two theories. Or as they put it: 'in order that the problem might be approached in some other ways' (Krogh & Krogh, 1909*a*). The 'other ways' referred to the use of CO to measure alveolar–capillary diffusion. The findings were eventually published in 1910 in a series of no less than seven papers (Gjedde, 2010). The final paper concluded that 'the absorption of oxygen and the elimination of carbon dioxide in the lungs takes place by diffusion and by diffusion alone. There is no trustworthy evidence of any regulation of this process on the part of the organism' (Krogh & Krogh, 1909*b*). However, the controversy over oxygen secretion *vs.* diffusion continued for many years. Indeed several expeditions were even undertaken by Haldane, Douglas, Barcroft and others to collect measurements of arterial P_{O_2} at high altitude in support of the different theories (West, 1996).

Careful measurements

The cornerstone of August and Marie's studies was the careful measurements they made. Marie in particular focused on obtaining data in healthy subjects (which included themselves) at different work rates. It is possible that her clinical training enabled her to see implications of their findings on both physiology and pathophysiology. She carried out many studies to establish the accuracy of her data within and between the subjects. In the seminal 1915 paper she describes:

> At first I found it impossible to obtain agreement between the figures for combustion and for CO_2 absorption. The apparatus was taken to pieces and cleaned from end to end and afterwards tested in every way imaginable, but the disagreement remained. At last I found out that the tap grease contained volatile combustible substances. It is only after introducing pure hogs lard as tap grease that I have obtained the desired accuracy [Krogh, 1915].

This point also offers an insight into the difficulty in performing the tests and may explain why they were not used much until the 1950s when post war the infra-red CO meter was available, a product of the need for gas detection during the war. The single breath D_{LCO} test was modified and standardised in 1957 (Ogilvie *et al.* 1957) and following developments by Robert E. Forster II (West, 1996) now forms the basis of every D_{LCO} test carried out today (Macintyre *et al.* 2005).

What happened next?

August Krogh went on to receive the Nobel Prize in 1920 for a series of studies describing the capillary circulation (Krogh, 1919*a*,*b*,*c*). Years later he reported that he had discussed his ideas with Marie, as his nearest colleague, throughout their life together. Marie went on to become a leading authority on nutrition in Denmark, while supporting her husband and family.

Mary Morrell (right) is Professor of Sleep and Respiratory Physiology in the National Heart & Lung Institute at Imperial College London, UK. Following a Fellowship at the University of Wisconsin-Madison, USA, she returned to the UK to set up the Unit of Sleep and Breathing with clinical colleagues at Royal Brompton Hospital, London. Its aim is to investigate the causes and consequences of sleep-related breathing disorders and translate research into improvements in patient care. Her current research focuses on the cardiovascular and neurological impact of sleep apnoea.

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Marie Krogh: female academic, clinician and mother

Marie Jorgensen decided at an early age to study medicine, reportedly burning her dolls in favour of serious literature. Despite family pressure to care for her widowed mother she entered The University of Copenhagen in 1901. Marie wrote in 1925:

> when I started my University studies 25 years ago, the road for women academicians was essentially paved. All academic societies were open to us, we were no longer a novelty and, on the other hand, we were still too few for competition to be a problem. In contrast to English and some American Universities, here at the Danish University, we had access to the same education, the same hospitals and clinics as the men [Schmidt-Nielsen, 1984]

Marie married August Krogh in 1905 and completed her medical degree in 1907. She then went on to defend her doctoral thesis in 1914 and published her seminal paper in 1915. These impressive achievements were combined with her family duties, having four children between 1908 and 1918 (two of which died during birth). At that time she wrote:

> For a number of years while the children were small, I had to adjust my work so that I could stay close to home. The practice of medicine had to wait. I was very fortunate, however, that our home and laboratory were in the same building, so that I with no difficulties could continue my laboratory research in combination with the teaching of physiology. [Schmidt-Nielsen, 1984]

It is reported that Marie had the help of nursemaids, but like all mothers there was a rule that if the children were hurt in any way she could be disturbed. Marie's daughter tells that they were always included in scientific discussions, and Marie is reported to have said that 'the good they have had nobody can take away from them'. Marie's daughter Bodil Schmidt-Nielsen went on to be an excellent physiologist, studying at the University of Copenhagen before moving to the States. A pioneer like her mother she became the first woman president of the American Physiological Society in 1975.

Marie Krogh's 1915 seminal paper is important in physiology in its own right. But, neither she nor her husband could have ever imagined that 100 years later it would be a mainstay in clinical pulmonary function testing throughout the world.

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Additional information

Competing interests

None declared.

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